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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/071,174	02/07/2002	John C. Reed	8014-014 US	2991
32301	7590	06/12/2008	EXAMINER	
CATALYST LAW GROUP, APC			ANGELL, JON E	
9710 SCRANTON ROAD, SUITE S-170				
SAN DIEGO, CA 92121			ART UNIT	PAPER NUMBER
			1635	
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			06/12/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/071,174	REED ET AL.	
	Examiner	Art Unit	
	J. E. Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 12 March 2008.

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1,4,12-14,17-23,25-28,76,77 and 152-163 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) 1,4,12-14,17-23,25-28 and 152-161 is/are allowed.

6) Claim(s) 76 and 162 is/are rejected.

7) Claim(s) 77 and 163 is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892)

2) Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____.

4) Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.

5) Notice of Informal Patent Application

6) Other: _____.

DETAILED ACTION

This Action is in response to the communication filed on 3/12/08.

The amendment filed 3/12/08 is acknowledged and has been entered.

Claims 1, 4, 12-14, 17-23, 25-28, 76, 77, 152-163 are currently pending in the application and are addressed herein.

1. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 76 and 162 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for producing a polypeptide in solution or *in vitro*, does not reasonably provide enablement for a method of producing a polypeptide *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,

“Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.”

The nature of the invention

The claims encompass making a polypeptide *in vivo* and encompass making the polypeptide as a therapeutic polypeptide *in vivo*, which encompasses gene therapy. As such, the invention is in a class of invention which the CAFC has characterized as “the unpredictable arts such as chemistry and biology.” *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The instant claims are broad in the sense that the claims merely recite a method of producing a polypeptide comprising expressing a nucleic acid encoding an amino acid sequence. Although the claims do not explicitly indicate that the polypeptide is produced *in vivo*, it is noted that dependent claims 77 and 163 indicated that the polypeptide is produced in solution or in a cell *in vitro*. Since the independent claims must be broader than the dependent claims, claims 76 and 162 can properly be considered to encompass producing the polypeptide *in vivo*.

Furthermore, given their broadest reasonable interpretation consistent with the specification, the claims encompass expressing the polypeptide in order to treat a disease.

The unpredictability of the art and the state of the prior art

The specification does not disclose that the methods have effectively treated any disease or disorder by administering a nucleic acid which encodes the protein and expressing the protein *in vivo* in order to obtain a therapeutic effect.

It is noted that the claims are not directed to the treatment of any particular disease; therefore, given the broadest reasonable interpretation, the claims encompass treating any disease or disorder.

At the time of filing, the relevant art considered gene therapy as a whole to be unpredictable. For instance, **Anderson** (Nature 1998; previously of record) teaches,

“The challenge is to develop gene therapy as an efficient and safe drug delivery system. The goal is more difficult to achieve than many investigators had predicted... The human body has spent many thousands of years learning to protect itself from the onslaught of environmental hazards, including the incorporation of foreign DNA into its genome. (See p. 25, second paragraph). The ultimate goal of gene therapy research is the development of vectors that can be injected, will target specific cells, will result in safe and efficient gene transfer into a high percentage of those cells, will insert themselves into appropriate regions of the genome (or will persist as stable episomes), will be regulated be either by administered agents or by the body’s own physiological signals, will be cost effective and will cure disease. (See p. 30, first paragraph).”

Dang et al. (Clin. Cancer Res. 1999; previously of record) teaches “Although significant progress has been achieved in our understanding of the limitations of gene therapy by suboptimal vectors, host immunological responses to the vectors, and the lack of long term stable expression, the major challenge that limits clinical translation remains in achieving efficient gene delivery to target tissues” (page 474, col. 2, last paragraph).

With respect to using the claimed method for treating a disease, it is noted that the claims encompass treating any disease. Therefore, given the broadest reasonable interpretation consistent with the specification, the claimed method can be interpreted as treating any disease associated with an abnormally high level of apoptosis such as diabetes by administering a polynucleotide encoding the anti-apoptotic polypeptide to a diabetic patient.

However, regarding gene therapy for diabetes, **Levine** (Mol. Med. Today 1999; previously of record) indicates many of the obstacles that need to be overcome in order to create an effective gene therapy for diabetes including gene transfer problems, cell transfer problems, and the responsiveness of the transduced cells to blood glucose levels. Levine focuses on gene transfer into pancreatic beta cells.

Regarding gene transfer into beta cells, Levine indicates that there are two general means by which therapeutic genes can be introduced into beta cells: by transducing the islet cells *ex vivo* and reintroducing the cells into the pancreas of the subject (see p. 165, last paragraph), and transfer of the therapeutic gene(s) into pancreatic beta-cells *in vivo*. However, Levine also indicates, “Successful islet cell transplantation has proved to be an elusive goal... (and) to date, there are no studies demonstrating that [in vivo gene transfer into beta-cells] can be done.” (See p. 166).

Levine teaches that both type I and type II diabetes results in the apoptotic death of beta-cells (see p. 166-167) and further indicates that preventing beta-cell apoptosis may be potentially

applicable to both type I and type II diabetes either by inhibiting apoptosis of beta cells before they die via gene transfer of anti-apoptotic genes such as Bcl-2 into the beta cells (e.g., see p. 168-169). However, gene transfer into beta cells is unpredictable as indicated above.

Furthermore, Levine also indicates that successful gene transfer into beta cells (either *in vivo* or *ex vivo*) and/or successful cell transplant are not the only obstacles to obstacle to overcome in order to effectively treat diabetes. Once the therapeutic gene(s) or cells are successfully delivered, the cells must be able to respond changes in blood glucose levels:

“A definitive treatment for diabetes mellitus will be one that maintains a normal blood glucose concentration in the face of fluctuating dietary intake. To accomplish this there must be mechanisms to sense the amount of blood glucose coupled to rapid release of the right amount of insulin.” (See p. 165, abstract).

Levine summarizes the state of gene therapy for diabetes by stating, “the ultimate goal of a definitive, permanent treatment of diabetes through gene therapy lies in the distant future.” (p. 170, last paragraph).

In view of the teachings of Anderson, Deng and Levine, it is clear that gene therapy methods are unpredictable in nature. Furthermore, the specification does not disclose working examples or provide guidance which would overcome the art-recognized problems. Therefore, additional experimentation would be required in order to practice the invention to the full scope encompassed by the claims.

Therefore, in view of the breadth of the claims, the limited amount of direction and/or guidance provided in the specification, as well as the art recognized unpredictability of gene therapy and the limited working examples, it is concluded that an undue amount of experimentation is required for one skilled in the art to make and use the claimed invention to the full scope encompassed by the claims.

Response to Arguments

2. With respect to the currently pending rejection(s), Applicant's arguments filed 3/12/08 have been fully considered but they are not persuasive.
3. Applicants argue that the claims do not explicitly recite that the polypeptide is produced *in vivo*. Applicants assert that the Examiner's statement that since dependent claims 77 and 163 indicate that the polypeptide can be produced in a cell *in vitro*, then it is proper to construe claims 76 and 162 as encompassing *in vivo* production, is erroneous because claims 77 and 163 indicate that nucleic acid expression rather than polypeptide production is performed *in vitro*. Applicants also contend, "[I]t is not reasonable to interpret the specification to include *in vivo* methodologies. Therefore, it is not reasonable to be required to amend the claims to expressly disclaim *in vivo* production of the subject polypeptide."
4. In response, it is acknowledged that the instant claims do not explicitly recite that the polypeptide is produced *in vivo*. However, it is proper to give the claims their broadest reasonable interpretation consistent with the specification. It is respectfully pointed out that the specification explicitly discloses *in vivo* embodiments of the instant claims. For instance, see page 3, lines 23-24, which states, "Invention nucleic acids can be expressed (e.g., transcribed

and/or translated) in solution or solid phase, or in cells tissue or organs *in vitro*, *ex vivo* or *in vivo*.” Page 5, lines 20-28, states, “Invention nucleic acids, polypeptides, antibodies and other compositions set forth herein may be expressed in animals, including non-human transgenic animals. In one embodiment, a non-human transgenic animal includes a polynucleotide sequence having at least about 70% identity to SEQ ID NO: 1.” Page 7, lines 20-28 states,

Methods of the invention further include modulating apoptosis in a subject. In one embodiment, a method includes administering to the subject an amount of Bcl-B polypeptide, a polynucleotide sequence having at least about 70% identity to SEQ ID NO: 1 or an antisense thereof, or a Bcl-B antibody sufficient to modulate apoptosis in the subject. Candidate subjects having or at risk of a disorder or pathological condition associated with apoptosis may be treated. Thus in another embodiment, a method includes administering to a subject having or at risk of a disorder associated with apoptosis with an amount of a Bcl-B polypeptide, a polynucleotide sequence having at least about 70% identity to SEQ ID NO: 1 or an antisense thereof, or a Bcl-B antibody sufficient to treat the subject having or at risk of a disorder associated with apoptosis.

5. Page 8, lines 1-10 states,

Subjects suffering or at risk of suffering from a disorder associated with apoptosis include those having a cell degenerative or proliferative disorders. Thus, disorders treatable in a method of the invention include, for example, a neoplasia, autoimmune disorder or fibrotic condition. In particular aspects, the disorder is characterized by neural or muscle degeneration, such as Alzheimer's disease, Parkinson's disease, Creutzfeldt-Jacob's disease (CJD), Huntington disease (HD), Machado-Joseph disease (MJD), Spinocerebellar ataxias 1, 2 and 6 (SCA-1, -2 and -6), dentatorubropallidolysian atrophy (DRPLA), Kennedy's disease, ischemia, stroke and head trauma, for example. In additional particular aspects, apoptosis or the disorder associated with apoptosis is present in one or more cells of heart, brain, lung, kidney, liver, pancreas, spleen, thymus, colon, muscle, leukocyte, small intestine, testis, prostate or ovary.

Therefore, the specification clearly contemplates expressing the claimed nucleic acid *in vivo*. In other words, the claims encompass producing the polypeptide *in vivo* by expressing the nucleic acid sequence which encodes the polypeptide *in vivo*. Thus, the claims have been given their broadest reasonable interpretation consistent with the specification. Furthermore, to clarify

the Examiner's statement to which Applicants take issue: independent claims must be broader in scope than all claims which depend therefrom; in this case the independent claim does not specify *in vivo* embodiments, however, the dependent claims clearly narrow the independent claims to nucleic acid expression in solution or in a cell that is *in vitro*; therefore, it is reasonable to interpret the independent claims as encompassing both *in vitro* (as explicitly recited in claims 77 and 163), as well as *in vivo* embodiments. Additionally, it is respectfully pointed out that nucleic acid expression *in vivo* would result in production of the polypeptide encoded by the nucleic acid *in vivo*.

Therefore, Applicants arguments as they pertain to the pending rejections are not persuasive.

Allowable Subject Matter

6. Claims 1, 4, 12-14, 17-23, 25-28, 152-161 are allowed.
7. Claims 77 and 163 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Monday-Thursday 8:00 a.m.-6:00 p.m. .

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J. E. Angell/
Primary Examiner, Art Unit 1635